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Abstract

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Project Title:	Homogeneous Flourescence Intensity High Throughput Assay for Cdc25B Phosphatase I

Abstract: *DESCRIPTION (provided by applicant):* Cdc25s are protein tyrosine phosphatases that control cell cycle progression. Of the three human isoforms that exist (Cdc25A, B, and C), Cdc25A and Cdc25B have been found to be oncongenic and over-expressed in many cancer cell lines. Cdc25B has been a target in multiple drug discovery endeavors, leading to several weak inhibitors of phosphatase activity. The majority of these compounds, however, are quinones, which inhibit Cdc25B catalytic activity through irreversible oxidation of the catalytic cysteine rather than specific binding at the catalytic domain. We propose to identify potent, selective, non-oxidizing inhibitors of Cdc25B. Initially, we used the catalytic domain of Cdc25B and a homogeneous fluorescence intensity assay to screen the MLSCN starter set of 3,316 compounds at 10 fM in a 384-well high throughput screen. The assay was robust with a Z' factor of > 0.5. In our preliminary studies, we identified a unique, non-quinone pharmacophore with an IC50 of 8.12 q 0.06. These results suggest that an evaluation of the NIH small molecule repository will identify a significant number of new lead compounds as inhibitors of Cdc25B.

Thesaurus Terms: Cdc25, protein tyrosine phosphatases, Cdc25A, Cdc25B, Cdc25C, drug discovery, cancer, inhibitors of phosphatase, quinones, Molecular Libraries Screening Centers Network, MLSCN, fluorescence intensity assay, 384-well plate format, high-throughput screening, HTS

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